REMARKS

In the instant Office Action, Claims 1-19, 21 and 29 are under prosecution. Claims 20, 22-28 and 30 stand withdrawn without prejudice due to a restriction requirement. Applicant reserves the right to pursue the so-withdrawn claims by way of divisional application(s), if Applicant chooses to do so.

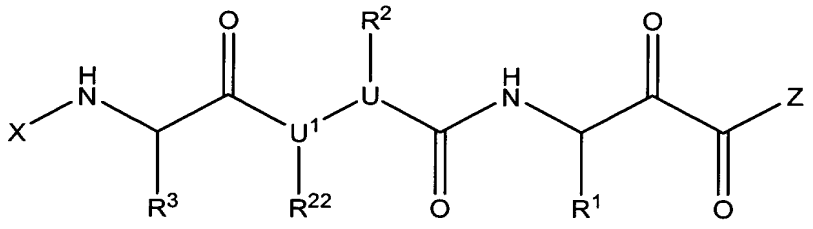
Claim 6 has been amended to reflect its proper dependency from Claim 5; Applicant regrets the typographical error.

In the Office Action, Claims 1-19, 21 and 29 were rejected under 35 U.S.C. § 101. Claims 1-19, 21 and 29 were rejected under 35 U.S.C. § 112, first paragraph, under "written description" grounds. Claims 1-19, 21 and 29 were rejected under 35 U.S.C. § 112, first paragraph, under "enablement grounds". Applicant respectfully traverses these rejections for the following reasons:

I. REJECTION OF CLAIMS 1-19, 21 AND 29 UNDER 35 U.S.C. § 101:

Claims 1-19, 21 and 29 are rejected under 35 U.S.C. § 101 because the instant claims are allegedly directed to non-statutory subject matter. The office Action alleges that the compounds of formula I read upon products found in nature. The Office Action suggests that claim 1 should be amended to incorporate that the compound has been "isolated" or "purified". Applicant disagrees with this rejection.

It is respectfully submitted that instant claim 1 is directed to a compound, including enantiomers, stereoisomers, rotomers and tautomers of the compound, and pharmaceutically acceptable salts, solvates or derivatives thereof, with said compound having the general structure shown in Formula I:



Formula I

where the variables are as described therein. Claims 2-16 depend from claim 1 and further define variables in formula I. Claims 17 and 18 are directed to specific compounds within the scope of formula I. Claims 19 and 21 are directed to compositions containing the compounds of formula I. Claim 29 depends from claim 17 and further defines the compounds recited therein. It is disclosed in the application that these compounds are inhibitors of the HCV protease. The application further discloses that the claimed compounds are α-ketoamide peptide analogs and generally contain eleven amino acid residues. There is a α-ketoamide group at the P1 position of the compounds. The compounds are capped at the N-terminus with an acyl, carbamoyl or sulfonyl group and are C-terminal amides, esters and acids. The application demonstrates procedures for preparation of compounds of formula I. Nowhere in the application it is mentioned that the compounds of the instant claims are natural products or are isolated from natural source. Therefore, the instant claims are not directed to compounds found in nature. All the compounds within the scope of the instant claims are compounds prepared in the laboratory, either by the procedures described in the application or by other equivalent procedures known to those of skill in the art.

Furthermore, the Office Action has not provided any art to support the allegation that the compounds of formula I read upon products found in nature. Applicant requests that if the Examiner is aware of any such art, then it should be made of record.

II. REJECTION OF CLAIMS 1-19, 21 AND 29 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR ALLEGED LACK OF WRITTEN DESCRIPTION:

Claims 1-19, 21 and 29 are rejected under 35 U.S.C. § 112, first paragraph for lack of written description. The Office Action alleges that the specification does not convey one of skill in the art that, at the time the application was filed, the inventors had possession of the enantiomers, stereoisomers, rotomers, tautomers, salts, solvates or derivatives of the compounds of formula I. The Office Action concludes that one of skill in the art would not recognize from the disclosure that applicant was in possession of the genus, namely enantiomers, stereoisomers, rotomers, tautomers, of

formula I, and pharmaceutically acceptable salts, solvates or derivatives, or any other SEQ ID NO of broad formula I. Applicant disagrees with this rejection.

Applicant respectively submits that an objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." The guidelines promulgated by the U.S. PTO for written description rejection recite:

In rejecting a claim, set forth express findings of fact regarding the above analysis which support the lack of written description conclusion. These findings should:

(1) identify the claim limitation not described; and

(2) provide reasons why a person skilled in the art at the time the application was filed would not have recognized the description of this limitation in view of the disclosure of the application as filed.

In this instance, there is no basis to conclude that a person skilled in the art at the time the application was filed would not have recognized the description of enantiomers, stereoisomers, rotomers, tautomers, salts, solvates or derivatives of the compounds of formula I in view of the disclosure of the application as filed.

Applicant respectfully submits that the specification as originally filed describes the compounds of formula I in great detail. All the variables in formula I are described in the specification on pages 7-23. The claims as originally filed claim enantiomers, stereoisomers, rotomers, tautomers, salts, solvates or derivatives of the compounds of formula I. A skilled artisan, based on the application disclosure would know what an enantiomer, stereoisomer, rotomer, tautomer, salt, solvate or pharmaceutically derivative of the compound of formula I is because such derivatives are routinely prepared and used in the art. A skilled artisan would also recognize sequences other than SEQ ID NO 5-52 within the scope of the claims because formula I and all the

variables therein are described in the application. The specification on page 23, line 25 through page 24, line 2 discloses exemplary pharmaceutically acceptable derivatives such as salts of compounds of formula I. The specification also discloses exemplary acids and bases suitable for salt formation. Further, it is not necessary to include in the specification that which those of skill in the art know. The specification is presumed to include all such knowledge. The Examiner is reminded that possession does not mean physical possession but appreciation. It is not necessary to make and test all or any embodiments to meet the written description requirement. The application as originally filed describes compounds of formula I in detail, exemplifies several compounds within the scope of formula I and claims compounds of formula I and enantiomers, stereoisomers, rotomers, tautomers, salts, solvates or derivatives thereof. In light of the foregoing, the present application clearly conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was in possession of the presently claimed subject matter.

Rebuttal to the specific allegations in the Office Action:

Structures or functions of compounds of the instant claims:

The Office Action alleges that with the substantial variability among the broad genus of formula I; enantiomers, stereoisomers, rotomers, tautomers, salts, solvates or derivatives or any other SEQ ID NO other 5-52, of broad formula I, it is not clear as to what such compound structures or functions are.

Structure:

As discussed above, the application provides general formula for compounds within the scope of the claims and claims enantiomers, stereoisomers, rotomers, tautomers, salts, solvates or pharmaceutically acceptable derivatives within the scope of formula I. The specification provides detail description of all the variables in formula I. Several exemplary compounds, including their structures (Table 1) within the scope of formula I are disclosed in the application. Furthermore, as discussed in detail below, a person of skill in the knows what enantiomers, stereoisomers, rotomers, tautomers, salts, solvates or pharmaceutically acceptable derivatives of a given compound are. Therefore, based on the disclosure in the application, a

skilled artisan would be able to appreciate other compounds within the scope of the instant claims.

Function:

Applicant respectfully submits that the function of the compound is irrelevant to the written description requirement. As discussed above, the objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed.". In the instant case, applicant clearly provides adequate written disclosure for the compounds instantly claimed. Moreover, application discloses that compounds of formula I are HCV protease inhibitors. Application provides assays to screen the compounds of formula I for the asserted activity. Application also provides HCV protease inhibitor activity data for several of the compounds within the scope of claim 1. Therefore, applicant respectfully submits that a person of skill in the art would recognize the structure and function of the compounds of formula I.

III. REJECTION OF CLAIMS 1-19, 21 AND 29 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR ALLEGED LACK OF ENABLEMENT:

Claims 1-19, 21 and 29 are rejected under 35 U.S.C. § 112, first paragraph because the specification, while being enabling for SEQ ID NOS:1-52, does not reasonably provide enablement for any compound that reads on broad formula I, enantiomers, stereoisomers, rotomers, tautomers of the compounds of formula I and pharmaceutically acceptable salts, solvates or derivatives thereof. The Office Action alleges that the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims. The Office Action notes that applicants have enabled compounds of SEQ ID NOS 1-52, as within broad Formula I but alleges that the compounds of SEQ ID NOS 1-52 are small peptides (11-mers) and even a slight change in the structure of a small peptide can drastically alter its native function. It is urged in the Office Action that factors such as stearic hindrance, change in polarity or conformation of the peptide leads to the change in the peptide

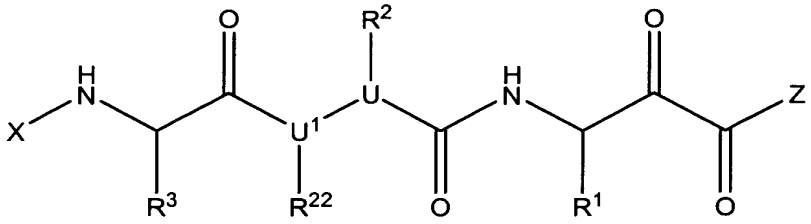
structure and can affect its native function. The Office Action concludes that based on the highly unpredictable and complex nature of peptide synthesis and function, determining which peptides could be made to correspond to the broad claim 1, encompassing enantiomers, stereoisomers, rotomers, tautomers of the compounds of formula I and pharmaceutically acceptable salts, solvates or derivatives thereof would require undue experimentation without a reasonable expectation of success by one of ordinary skill in the art. Applicant disagrees with the rejection.

Applicant respectfully submits that the inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). As instructed in the published PTO guidelines, it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The analysis must consider all the evidence related to each of the factors, and any conclusion of non-enablement must be based on the evidence as a whole. *Id.* 8 USPQ2d at 1404 & 1407.

Applying the above factors to the instant claims, applicant respectfully submits that, as described in detail below, it would not require undue experimentation to practice the full scope of the claimed subject matter.

Scope of the claims:

Claim 1 is directed to compounds, including enantiomers, stereoisomers, rotomers, tautomers, salts, solvates or derivatives of thereof, wherein the compound has formula I



Formula I

where the variables are as described therein. Claims 2-16 depend from claim 1 and further define the variables in formula I. Claims 17 and 18 are directed to specific peptides within the scope of formula I. Claim 19 is directed to a pharmaceutical composition containing compound of claim 1. Claim 21 further defines composition of claim 19. Claim 29 depends from claim 17 and is directed to a compound, including enantiomers, stereoisomers, rotomers, tautomers, salts, solvates or derivatives of thereof, exhibiting HCV protease inhibitory activity. As discussed above, compounds of formula I are described in the application on pages 7-23. Furthermore, a person of skill in the art knows what enantiomers, stereoisomers, rotomers, tautomers, salts, solvates or pharmaceutically acceptable derivatives of compounds of formula I are. A skilled artisan can easily choose appropriate starting materials to prepare such compounds within the scope of claim 1. Therefore, the scope of the claims is not broader than the application disclosure.

The level of skill in the art is high:

The level of skill in this art is recognized to be high (see, e.g., Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). In addition, the numerous articles and patents that are of record in this application that are authored by those of a high level of skill for an audience of a high level of skill further evidences the high level of skill in this art.

Knowledge of those of skill in the art:

At the time of the effective filing date of this application and before, a large body of literature has been published in the area of peptide chemistry. A skilled artisan knew, based on the literature available, what enantiomers,

stereoisomers, rotomers, tautomers and pharmaceutically acceptable salts, solvates or derivatives of a given compound are. For example, "Organic Chemistry" by F. A. Carey and Merriam-Webster dictionary define these terms as follows:

Stereoisomers: Isomers that have the same constitution but differ in the spatial arrangement of their atoms are called stereoisomers.

Enantiomers: Stereoisomers that are related as an object and its nonsuperimposable mirror image are classified as enantiomers.

Rotamers: An isomer differing from other conformation(s) only in rotational positioning of its parts, such as *cis*- and *trans*- forms.

Tautomers: Isomers obtained by interconversion between two structures that differ by the placement of an atom or group.

Solvate: An aggregate that consists of a solute ion or molecule with one or more solvent molecules.

Further, there is a multitude of literature that teaches a skilled artisan reactions in peptide synthesis and how to prepare various isomers and derivatives discussed above. For example, M. Bodanszky in "*Principles of Peptide Synthesis*" discusses and exemplifies reaction conditions for preparation of L and D-enantiomers for several peptides citing numerous references. A skilled artisan would know from the literature how to prepare any particular isomer or derivative within the scope of the instant claims. Further, it is known in the art that pharmaceutically acceptable derivatives of a compound include salts, esters, enol ethers, enol esters, acetals, ketals, orthoesters, hemiacetals, hemiketals, acids, bases, solvates, or hydrates thereof. Such derivatives can be readily prepared by those of skill in this art using known methods for such derivatization. A skilled artisan would be able to select appropriate starting material and reaction conditions to arrive at a particular isomer or pharmaceutically acceptable derivative of a given compound because such reactions are routinely performed in the art.

The teachings in the specification and presence of working examples:

The specification describes the compounds of formula I on pages 7-11. All the variables in formula I are clearly and explicitly described in the specification. The specification discloses several exemplary compounds

within the scope of formula I on pages 41-44. The specification demonstrates a general procedure for the preparation of compounds of formula I by describing all the steps involved. The specification, on pages 32-41 describes application of this general procedure to synthesize an exemplary compound, Ac-Glu-Glu-Val-Val-Pro-Val-(CO)-Gly-Met-Ser-Tyr-Ser-NH_2, within the scope of the instant claims. The specification discloses that the compounds within the scope of claim 1 may also be prepared by any other procedure known to those of skill in the art. The specification discloses that the compounds are inhibitors of the HCV protease and are used in compositions and methods for treatment, prevention or amelioration of one or more of the symptoms of hepatitis C. The specification describes assays to screen the compounds for HCV protease inhibitory activity on pages 44-48. The activity data for several of the compounds within the scope of the instant claims is provided in Table 1. Further, the specification describes examples of pharmaceutically acceptable derivatives of compounds of formula I including salts of the compounds of formula I, and discloses, on page 23, line 25 through page 24, line 2, exemplary acids and bases suitable for formation of such pharmaceutically acceptable salts. Based on the detailed procedure described in the application and routine reactions in chemistry, a skilled artisan would be able to choose appropriate starting materials to prepare the compounds within the scope of the instant claims without undue experimentation. Further, such compounds can be screened by the assays described in the application for the desired utility. Therefore, the application provides sufficient guidance for one of skill in the art to make and use the full scope of the claimed subject matter.

IV. CONCLUSION:

In light of the scope of the claims, the description in the application, the high level of skill of those in this art, and the extensive knowledge of those of skill in this art, it would not require undue experimentation to practice full scope of the claims.

The Examiner is reminded that applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art

could obtain by virtue of that which the applicant has disclosed. It would be unfair and unduly limiting to require applicant to limit the claims to the exemplified compounds of SEQ ID Nos 5-52 when the specification clearly places those of skill in the art in possession of compounds of formula I as instantly claimed. Therefore, it would be unfair, unduly limiting and contrary to the public policy upon which the U.S. patent laws are based to require applicant to limit the claims only to the exemplified species:
See, e.g., In re Goffe, 542 F.2d 801, 166 USPQ 85 (CCPA 1970):

"for the Board to limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the claims can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists to promote progress in the useful arts".

"The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions" In re Sus and Schafer, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

To require applicant to limit the claims to only the exemplified compounds of SEQ ID NOs 5-52 would permit those of skill in the art to practice what is disclosed in the application, including enantiomers, stereoisomers, rotomers, tautomers, salts, solvates or derivatives of compounds of formula I, but avoid infringing such limited claims. One of skill in the art could readily prepare enantiomers, stereoisomers, rotomers, tautomers, salts, solvates or derivatives of compounds of formula I by using the procedures described in the application and screen them using the Serine Protease Inhibitor assay as taught in the specification. The first paragraph of §112 requires only that the disclosure be sufficient to teach one of skill in the art how to make and use the claimed subject matter without undue experimentation. As discussed above, the specification discloses a general procedure and application of the general procedure to synthesize several exemplary compounds within the scope of the instant claims. Based upon the application disclosure, those skilled in the art can prepare other compounds

within the scope of the claims and screen them using the assays described in the application.

Further, a patentee not only is entitled to narrow claims particularly directed to a specific embodiment, but also to broad claims that define an invention without a reference to specific instrumentalities. *Smith v. Snow*, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935). As discussed above, applicant has described the general formula for compounds within the scope of claim 1, a general procedure with specific examples to prepare such compounds and assays to screen the compounds. Based on this disclosure and with little experimentation a person of skill in the art can practice full scope of the instant claims.

Rebuttal to Specific Arguments in the Office Action:

Applicant herein provides response to the specific issues raised in the office action.

1. Broad scope:

The Office Action states that the applicants have reasonably taught and/or demonstrated SEQ ID NOS: 1-52, as within broad Formula I. The Office Action alleges that broad claim 1 encompasses any and all enantiomers, stereoisomers, rotomers and tautomers of the compound, and pharmaceutically acceptable salts, solvates or derivatives of broad Formula I. It is urged in the Office Action that factors such as stearic hindrance, change in polarity or conformation of the peptide leads to the change in the peptide structure and can affect its native function.

Applicant respectfully submits that as discussed in detail above, preparation of enantiomers, stereoisomers, rotomers and tautomers and pharmaceutically acceptable salts, solvates or derivatives of a given compound involve routine modifications to the reaction protocols disclosed in the application. A skilled artisan is well aware of various starting materials and reaction conditions to arrive at a particular derivative within the scope of the instant claims. Applicant agrees with the Office Action that stearic hindrance, change in polarity or conformation of the peptide leads to the change in the peptide structure and can affect its native function. However, it is respectfully submitted that the application describes assays to screen the

compounds for the HCV protease inhibitory activity. The application also provides activity data for several of the compounds within the scope of the claims. A person of skill in the art would be easily able to screen various isomers and derivatives within the scope of the claims with little experimentation for the desired activity.

There being no other rejection pending, Applicant believes that the claims, as amended, are in allowable condition. Such an action is earnestly requested. If the Examiner has questions, the Examiner is invited to contact the undersigned.

September 17, 2003
Patent Department, K-6-1,1990
Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033
Tel: (908) 298-5068
Fax: (908) 298-5388

Respectfully submitted,

Dr. Palaiyur S. Kalyanaraman
Attorney for Applicants
Reg. No. 34,634